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BRIEF REPORT

Vein wall remodeling in patients with acute deep vein thrombosis and chronic postthrombotic changes

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Essentials

- This study examined vein wall remodeling in acute thrombosis and postthrombotic syndrome (PTS).
- Thrombus-wall interface was measured using ultrasound real-time high definition zoom.
- Experimental cohorts demonstrated increased vein wall thickness localized to affected segments.
- Presence of thrombus or PTS are the most important factors affecting wall thickening.

Summary. *Introduction:* A few studies have investigated venous wall remodeling after venous thrombosis by using rodent models. Such information is lacking in humans. This study was designed to determine the acute and chronic effects of thrombus on the vein wall. *Methods:* Patients aged > 16 years with deep vein thrombosis diagnosed by duplex ultrasound were assessed by the use of case–control methodology. Those with recurring thrombotic episodes, cardiorespiratory disease, terminal cancer, morbid obesity, penetrating trauma or significant inflammation were excluded. High-resolution ultrasound was employed to determine wall thickness, with strict quality criteria and inclusion of only technically adequate ultrasound images. *Results:* Data were collected from patients with acute thrombosis (35), patients with chronic postthrombotic changes (15), and unaffected controls (32), with 853 total vein segments being analyzed. As compared with controls (mean 0.37 mm; 95% confidence interval [CI] 0.37–0.38 mm), venous wall thickness was increased in acute (mean 0.63 mm; 95% CI 0.61–0.64 mm) and postthrombotic (mean 0.85 mm; 95% CI 0.80–0.91 mm) venous segments. Ipsilateral, contralateral and unaffected control vein segments were not different. Ipsilateral segments were thicker than controls in postthrombotic syndrome (PTS) patients, but not in acute patients. Multiple regression analyses demonstrated small impacts of age and sex on vein wall thickness. *Conclusions:* Wall thickness increases in all lower-tcglimb venous segments of patients with acute and postthrombotic disease. Age and sex may affect wall thickness, although further investigation is required to clarify their impact. The equivalence of ipsilateral and unaffected control segments suggests that acute vein wall remodeling is mediated through direct interaction with the thrombus, whereas remodeling in PTS patients may be affected by other factors.

Keywords: doppler ultrasonography; postthrombotic syndrome; vascular remodeling; vein; venous thrombosis.

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Introduction

Thrombus formation is accompanied by an inflammatory response that remodels the thrombus itself and the venous wall. The thrombus may partially or completely resolve, and there may be partial or complete embolization of the thrombus. When the thrombus does not completely resolve, luminal changes resulting from subsequent collagen formation are seen. Common sequelae include postthrombotic syndrome (PTS) [1] and deep vein thrombosis (DVT) recurrence [2]. One proposed factor associated with these sequelae is vein wall remodeling [3].

The inflammatory process that mediates vein wall remodeling has been investigated in animal models, with several key molecules being identified. Several processes, including thrombus–wall interactions, and thrombus and venous wall remodeling, remain incompletely elucidated. To date, one small pilot study has examined venous wall changes following acute DVT in humans [4]. However, this study did not focus on wall changes, and examined only proximal lower-limb veins (popliteal, femoral, and common femoral) in a population containing possible confounding comorbidities.

The present study was designed to investigate venous wall thickness in patients presenting with acute thrombosis and PTS wall changes as compared with that of unaffected vein segments.

Methods

Study design

Patients aged > 16 years with signs and symptoms of acute DVT or PTS presenting to the non-invasive vascular laboratory at our institution between May 2012 and February 2016 were prospectively assessed for study inclusion. Institutional Review Board approval was obtained. Study participants with major comorbidities, including cardiorespiratory disease (right heart failure, cor pulmonale, or low ejection fraction heart failure), terminal cancer (metastatic or < 6-month prognosis), penetrating trauma, body mass index (BMI) of > 35, or significant inflammation (i.e. rheumatoid arthritis, systemic lupus erythematosus, etc.) were excluded. Patients with a previous history of surgical interventions for venous disease or bypass operations were also excluded.

Patients were classified into two groups according to well-established criteria of thrombus echogenicity, compressibility, vein diameter changes, and acuity of patients' signs and symptoms [4–6]. These groups were: (i) acute DVT (dilated vein, non-compressible, and homogeneous luminal material with smooth borders) in patients with signs and symptoms of ≤ 1 week in duration; and (ii) patients with chronic luminal changes (normal or reduced vein diameter, echogenic luminal material, and irregular borders and flow channels) and ultrasound-confirmed DVT at least 6 months previously. Unaffected segments contralateral and ipsilateral to the thrombosed segment were assessed when available, to serve as control measurements and to minimize bias resulting from inherent differences in vein morphology among individuals. Patients with signs and symptoms of DVT without thrombus or history of a thrombus were included as unaffected control patients. These patients were enrolled consecutively until a sufficient sample size was reached, with an initial goal of 30 patients.

Ultrasound measurements

All studies were performed in a non-invasive vascular laboratory (fully accredited by the Intersocietal Accreditation Commission) by registered vascular technologists with scanning experience of > 1500 lower-extremity venous examinations. A standard, bilateral lower-extremity ultrasound protocol was used to assess for thrombus. In instances of vascular malformation, penetrating trauma, and/or significant inflammation, only a unilateral limb examination may have been completed. Differentiation between the thrombus and the vessel wall was performed by the use of established parameters: the vessel wall is generally brighter (hyperechoic) than the incident thrombus. Only instances with a clear transition between the hypoechoic thrombus and hyperechoic vessel wall were included. Segments with poor thrombus–vein wall interfaces resulting from the interference of the thrombus or postthrombotic scarring were excluded. Measurements in which the vessel depth was > 6 cm, there was an inappropriate angle of insonation, and calcification from adjacent artery prevented accuracy were excluded. Postthrombotic patients with complete vessel occlusion by thrombus were excluded because of an inability to clearly visualize vein wall boundaries.

Veins imaged included the common femoral, femoral (proximal, middle, and distal), popliteal (proximal and distal), peroneal and posterior tibial. Gastrocnemial and soleal veins were included when possible. Each segment was examined with a 5–17-Hz multifrequency linear array transducer (iU22; Philips, Bothell, WA, USA). If the resolution was not optimal, owing to depth, a 5–12-MHz linear array was used. Curvilinear array transducers were not used, as their resolution is not adequate for vein wall measurements.

Venous wall measurements

Real-time high-definition zoom was used in all venous segments measured to assess the thrombus–wall interface (Fig. 1). Venous wall thickness is best measured at right angles with sharp wall definition by use of a high-resolution linear array transducer. The best acoustic window to give a sharp vein wall image is obtained by using multiple angles, heel-toeing the transducer, and applying optimal pressure without reducing the lumen diameter while avoiding slice thickness and off-beam artefacts. Vessel wall thickness measurements were performed by N.L., A.C., and J.G. Reviewers were blinded to the patient's indication for ultrasound examination and the results of the examination. For each venous segment, measurements were taken in triplicate, and the average value was used. The authors have previously performed extensive reproducibility studies on the venous wall measurements, with low variability in unaffected controls and those with chronic venous disease [7].

Statistical analysis

All continuous variables were assessed by ANOVA with the Bonferonni correction for pairwise comparisons and unpaired double-sided *t*-tests. As measurements were performed without an *a priori* hypothesis, measurements are reported as 95% confidence intervals (CIs). Multiple regression analysis was performed to examine the relationship between vein wall thickness and several potential predictors. SPSS STATISTICS 22 software (IBM Corporation, Armonk, NY, USA) was used for data analysis.

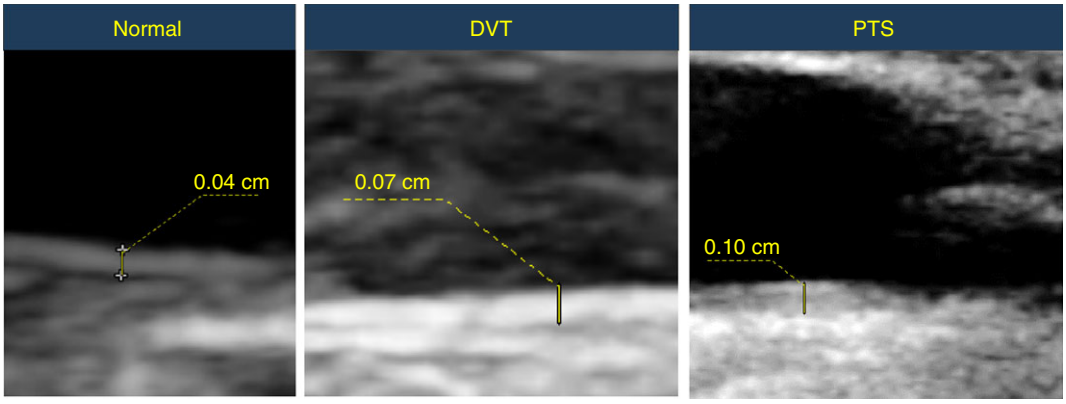

Fig. 1. High-resolution ultrasound images demonstrating significant wall thickening in patients with acute deep vein thrombosis (DVT) and postthrombotic syndrome (PTS) as compared with normal. [Color figure can be viewed at wileyonlinelibrary.com]

Results and discussion

There were 82 patients and 853 individual measurements. The demographics of the population and a breakdown of vein segment measurements by type and segment are shown in Table 1. All cohorts were well matched for age and sex, with the exception of there being a smaller number of females in the PTS group.

Overall, the mean wall thickness of acute DVT venous segments was 0.63 mm (95% CI 0.61–0.64 mm), that of PTS segments was 0.85 mm (95% CI 0.80–0.91 mm), and that of control segments was 0.37 mm (95% CI 0.37–0.38 mm). Acutely thrombosed and PTS vein segments were, on average, 69% and 129% thicker than control segments, respectively. Ipsilateral control segments (mean 0.38 mm, 95% CI 0.37–0.39 mm), contralateral control segments (mean 0.37 mm, 95% CI 0.36–0.38 mm) and normal control segments (mean 0.37 mm, 95% CI 0.36–0.38 mm) had comparable wall thicknesses.

There was a difference in venous wall thickness between control, acute DVT and PTS segments, as shown in Table 2. Moreover, proximal veins were thicker than calf veins in acutely thrombosed, PTS and unaffected veins (Table 2). The vein wall thicknesses of acute DVT and PTS proximal veins were 27% and 36% greater than those of the correspondingly affected calf segments. Among control segments, proximal veins were 19% thicker on average. Acutely thrombosed proximal and distal vein wall measurements were, respectively, 74% and 61% thicker than control segments, and PTS proximal and distal vein segments were, respectively, 128% and 100% thicker than control segments. The increase in vein wall thickness remained the same in the presence of a single DVT/PTS or bilateral DVT/PTS (Table 3).

Unaffected vein segments in PTS patients (mean 0.40 mm, 95% CI 0.39–0.41 mm, $n = 66$) were thicker than those in unaffected controls (mean 0.37, 95% CI 0.36–0.38, $n = 350$). This was not observed in unaffected vein segments of acute DVT patients. These findings may suggest that, in a chronic setting, the effect of thrombosis on the venous wall is beyond its original extent. This could happen because the veins may develop reflux at the site of thrombosis and remotely, or because asymptomatic thrombi develop subsequent to the original event [4,8–10].

Multiple regression analysis among control patients indicated a weak association (adjusted $r^2 = 0.31$) with a

Table 1 Patient demographics and measured venous segment frequency

	No. of patients		
	DVT	PTS	Control
	35	15	32
Female, no. (%)	19 (54.3)	4 (26.7)	17 (53.1)
Age (years), mean (SD)	60 (19)	59 (16)	54 (21)
Bilateral presentation, no. (%)	6 (17.1)	2 (15.4)	–

	No. of segments				
			Control		
	DVT	PTS	Ipsilateral	Contralateral	Volunteers
Mean no. of vessel segments (per patient)	4.4	5.2	3.9	2.9	11.1
Common femoral	19	6	29	11	50
Proximal femoral	18	5	0	8	51
Mid-femoral	16	4	22	7	47
Distal femoral	16	12	36	10	45
Proximal popliteal	16	20	25	16	45
Distal popliteal	18	20	18	14	45
Posterior tibial	19	5	8	9	40
Peroneal	20	6	7	9	39
Gastrocnemius	6	0	20	2	2
Soleal	6	0	1	3	2
Total	154	78	166	89	366

DVT, deep vein thrombosis; PTS, postthrombotic syndrome; SD, standard deviation.

Table 2 Vein wall thickness measurements

	Acute DVT			PTS			Control		
Vein segment	*N*	Mean (mm)	95% CI (mm)	*N*	Mean (mm)	95% CI (mm)	*N*	Mean (mm)	95% CI (mm)
Common femoral	19	0.74	0.70–0.77	6	1.02	0.81–1.22	90	0.42	0.41–0.43
Proximal femoral	18	0.68	0.65–0.70	5	0.91	0.83–0.99	59	0.38	0.37–0.39
Mid-femoral	16	0.66	0.64–0.68	4	0.89	0.71–1.07	76	0.38	0.37–0.39
Distal femoral	16	0.68	0.64–0.71	12	0.88	0.75–1.01	91	0.39	0.38–0.40
Proximal popliteal	16	0.66	0.63–0.69	20	0.93	0.79–1.06	86	0.39	0.38–0.40
Distal popliteal	18	0.67	0.64–0.70	20	0.81	0.71–0.90	77	0.39	0.37–0.40
Posterior Tibial	19	0.53	0.51–0.54	5	0.65	0.54–0.73	57	0.31	0.29–0.32
Peroneal	22	0.53	0.50–0.55	9	0.66	0.62–0.77	59	0.31	0.29–0.32
Proximal	103	0.68	0.67–0.69	67	0.89	0.84–0.94	515	0.40	0.39–0.40
Calf	51	0.52	0.51–0.53	11	0.66	0.59–0.72	106	0.32	0.31–0.33

CI, confidence interval; DVT, deep vein thrombosis; PTS, postthrombotic syndrome.

Table 3 Venous wall measurements of bilateral deep vein thrombosis (DVT)/postthrombotic syndrome (PTS) and unilateral DVT/PTS segments

Venous segments	*N*	Mean (mm)	95% CI (mm)
Acute DVT			
Proximal			
Bilateral DVT	31	0.70	0.67–0.72
Unilateral DVT only	72	0.68	0.66–0.69
Calf			
Bilateral DVT	14	0.51	0.49–0.53
Unilateral DVT only	37	0.52	0.51–0.54
PTS			
Proximal			
Bilateral PTS	12	0.86	0.75–0.97
Unilateral PTS only	55	0.89	0.83–0.96
Calf			
Bilateral PTS	0	–	–
Unilateral PTS only	11	0.64	0.59–0.72
Control			
Proximal			
Bilateral DVT/PTS	30	0.41	0.40–0.42
Unilateral DVT/PTS only	166	0.39	0.38–0.40
Calf			
Bilateral DVT/PTS	11	0.29	0.27–0.32
Unilateral DVT/PTS only	48	0.32	0.31–0.33

CI, confidence interval.

small effect (*B*-values: 0.002, 95% CI − 0.006 to 0.010 [sex]; 0.00064, 95% CI 0.0004–0.0008 [age]; − 0.0034, 95% CI − 0.011 to 0.004 [side]; 0.07, 95% CI 0.060–0.077 [location]). The presence of DVT or PTS (adjusted $r^2 = 0.797$) had the highest impact (*B*-values: 0.26, 95% CI 0.24–0.26 [DVT]; 0.47, 95% CI 0.45–0.49 [PTS]) on wall thickening. An age-dependent increase in the wall thickness of the great saphenous vein was documented in a recent article from our center [7]. These results suggest an age-dependent increase in venous wall remodeling leading to thicker and stiffer veins. The increases in vessel wall thickness and stiffness have been proposed to predispose older adults to recurrence and embolization [11].

This is the first comprehensive large prospective study in humans to assess the effect of thrombosis on the walls of the deep veins. Patients with conditions that could potentially alter the venous architecture were excluded. Vein wall thickness was greatest in segments with PTS changes, followed by acutely thrombosed and control segments. These differences were maintained across all venous segments examined.

Our findings are in agreement with the only previous small study of venous wall changes following thrombosis [4]. This study was limited to examining proximal vein segments at 6 months. It determined vein wall thickening of 50% in acutely thrombosed segments and 90% in PTS segments, as compared with 69% and 129%, respectively, in the present study. Our study investigated predetermined sections of the proximal veins for venous wall changes across all cohorts, in order to assess segment-specific changes in wall thickness. Calf veins constituted a minority of the measured segments in this study; however, this analysis offers evidence that these veins respond similarly to proximal veins. The 'chronic' stage in our study was any evaluation > 6 months following acute DVT diagnosis spanning to several years. This was chosen to better represent the effect of thrombus and vein wall remodeling in PTS patients.

The initial remodeling event is probably attributable to an acute inflammatory response associated with DVT formation, as suggested by gadolinium magnetic resonance venography [12]. In this study, enhancement of the venous wall at sites of thrombosis suggested extravasation. Gadolinium did not enhance the wall in PTS patients, however, indicating a different long-term mechanism for the wall thickening. One recent study examining tissue causing PTS via endophlebectomy noted chronic luminal changes composed of type I (80–90%) and type III collagen (10–20%), with the greatest density of collagen being seen at areas where the thrombosis made contact with the vein wall [13]. Non-contrast magnetic resonance imaging and ultrasound imaging corroborated these findings [14]. Preliminary results in acute DVT and PTS patients following intravascular ultrasound (IVUS) imaging (unpublished data from an ongoing study) also

support the above findings. For IVUS imaging, a catheter is placed directly inside the lumen of the vessel, to obtain images at the shortest possible distance. This method has less attenuation and therefore superior resolution to transcutaneous ultrasound. Altogether, a preponderance of evidence suggests that an ongoing interaction between vein wall and thrombus affects the ultimate outcome of thrombosis.

The clinical importance of vein wall remodeling is unclear. We hypothesize that the extent of remodeling following complete or partial recanalization of the DVT may predispose patients to reflux, obstruction, thrombus recurrence, PTS, and/or chronic venous disease. The findings in this study may prove useful clinically for establishing previous asymptomatic DVT, as a predictor of valvular function post-thrombosis, or as a means of determining the efficacy of thrombus-lysing agents.

This was a prospective study; however, it did not interfere with usual care, so patient enrollment was subject to clinical decision-making. Patients were not examined at the same time point in the acute and PTS groups. Owing to the observational nature of this study, patients in the PTS group were not examined at structured intervals (i.e. 6 months and 12 months). Only patients with symptomatic DVT were enrolled in this study. Luminal diameter, provoked/unprovoked status, BMI, and height, among other variables, were not examined in this study as possible variables effecting postthrombotic vein wall remodeling. Anticoagulation therapy, use of compression stockings and any other management strategies varied between patients, and were not examined. Although the ultrasound findings are compelling, no histologic validation was performed, as deep veins cannot be removed. Murine models of vascular thrombosis may present an opportunity for future research to assess pertinent histologic variations along the affected segments.

Overall, this prospective clinical study shows that both acute DVT patients and PTS patients had an increase in vein wall thickness localized to the affected segments as compared with controls. However, further research is required to understand the role and interplay of the specific chemical and cellular mediators involved in these remodeling events.

Addendum

A. Chandrashekar, J. Garry, A. Gasparis, and N. Labropoulos contributed to study design, writing, and editing of the manuscript. A. Chandrashekar and N. Labropoulos completed data abstraction. A. Chandrashekar, J. Garry, and N. Labropoulos contributed to data analysis.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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